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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 03/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/035,958	DESNOYERS ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 Dec 2001, 4 Sep 2002, 14 Oct 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-27 and 30-34* is/are rejected.

7)☒ Claim(s) *28 and 29* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3 May 2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendments filed 26 December 2001 and 4 September 2002 have been entered. Claims 22 – 34 are under examination.

Priority

35 U.S.C. § 119(e) states that:

> An application for patent filed under section 111(a) or section 363 of this title for an invention disclosed in the manner provided by the first paragraph of section 112 of this title in a provisional application filed under section 111(b) of this title, by an inventor or inventors named in the provisional application, shall have the same effect, as to such invention, as though filed on the date of the provisional application filed under section 111(b) of this title, if the application for patent filed under section 111(a) or section 363 of this title is filed not later than 12 months after the date on which the provisional application was filed and if it contains or is amended to contain a specific reference to the provisional application.

The preliminary amendment filed 4 September 2002 indicates that this application is a continuation of 09/931836, which is a continuation of PCT/US00/05601, which claims priority to provisional application 60/131270, filed 27 April 1999. While applicant disclosed the nucleic acid sequence in said provisional application, no use for either the nucleic acid or the encoded protein was disclosed.

Applicant is advised that the instant application can only receive benefit under 35 U.S.C. § 119(e) from an earlier application which meets the requirements of 35 U.S.C. § 112, first paragraph, with respect to the now claimed invention. Because the provisional application filed 27 April 1999 does not meet the requirements of 35 U.S.C. § 112, first paragraph, it is unavailable under 35 U.S.C. § 119(e). The effective priority date of the instant application is considered to be the filing date of the international application PCT/US00/05601, filed 1 March 2000.

Should applicant argue that the provisional application filed 27 April 1999 in fact is an enabling disclosure, applicant should provide reasoning as to why the provisional application is an enabling disclosure. For example, this could be accomplished by indicating the page and line numbers where PRO4408 was found to test positive in assay number 107, Fetal Hemoglobin Induction in an Erythroblastic Cell Line.

Information Disclosure Statement

The information disclosure statement filed 3 May 2002 has been considered. The database search results demonstrate that applicants are aware of nucleic acids with identity or

homology to the one claimed herein. However, as the BLAST results do not give sufficient identifying information, the examiner cannot determine if said sequences constitute prior art.

Specification

The disclosure is objected to because of the following informalities:

The title is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The specification includes browser-executable hyperlinks. This objection could be overcome by deleting all occurrences of the text "http://".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22 – 27 and 30 - 34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide with SEQ ID NO:61 that that are useful for making antibodies or can induce the switch from adult hemoglobin to fetal hemoglobin in an erythroblast cell line, does not reasonably provide enablement for polypeptides 80%, 85%, 90%, 95%, or 99% identical to SEQ ID NO:61. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731 737, 8 USPQ2d 1400 1404 (Fed. Cir. 1988).

The claims are directed to isolated polypeptides having at least 80% identity to a SEQ ID NO:61 with or without its signal peptide, or to polypeptides at least 80% identical to the

extracellular domain of SEQ ID NO:61 with or without its signal peptide. Dependent claims are directed to chimeric polypeptides.

The specification (p. 151, line 35 – p. 152, line 1) teaches that the nucleic acid encoding PRO4408 has (unspecified) homology to the nucleic acids which encode P_R27897, P_R49942, PBP_RAT, CELF40A3_3, D1ONCVO, PC4214, OV16_ONCVO, P_R27718, GEN10789, and OBA5_DROME, however the instant specification fails to indicate the degree of homology thereto, or whether the homology observed at the nucleic acid level even exists at the amino acid level. The specification (Figure 30) discloses several important features of the amino acid sequence, but does not indicate the presence of a transmembrane domain, nor which end of the that the amino acid sequence might be intracellular domain and which might be the extracellular domain if in fact the protein is a transmembrane protein.

The Examiner has determined that polypeptides identical to PRO4408 meet the utility requirements of 35 U.S.C. § 101, because the protein can be used to induce fetal hemoglobin in an erythroblastic cell line, which is useful to treat sickle-cell anemia. However, the claims encompass an unreasonable number of inoperative polypeptide sequences, which the skilled artisan would not know how to use. As opposed to the claims, what is disclosed about PRO4408 is narrow: a single polypeptide with the ability to induce fetal hemoglobin in an erythroblastic cell line.

There are no working examples of polypeptides less than 100% identical SEQ ID NO:61 which have the same activity as PRO4408, i.e. the ability to induce fetal hemoglobin. The examiner has determined that only one of the asserted utilities is sufficient to meet the requirements of 35 U.S.C. § 112, first paragraph. While the specification generally describes properties of cytokines, it is acknowledged that cytokines are diverse in function and structure. The specification does not provide guidance for using polypeptides related to (i.e., 80%-99% identity) but not identical to SEQ ID NO:61 which do not have the activities that PRO4408 is asserted to have. However, the instant specification discloses a single isolated polypeptide sequence SEQ ID NO:61.

Furthermore, protein function cannot be reliably predicted from sequence homology. For example, Transforming Growth Factor (TGF-beta) Family OP-1 induces metanephrongenesis whereas closely related TGF-beta family members-BMP-2 and TGF-beta1-have no effect on metanephrogenesis under identical conditions (Vukicevic et al., 1996, PNAS USA 93:9021-9026). TGF-beta has recently been found to play a role in signaling that induces the switch

from adult to fetal hemoglobin (Miller, 2002. Current Opinion in Hematology 9:87-92; see especially the section entitled Signals beginning on p. 89), and therefore the prior art teachings of Vukicevic on the ability of subtle changes to affect protein function are relevant. Additonally, the post-filing teachings by Liu et al. (2005. Journal of Biological Chemistry 280:7452-7459) indicates that in order to silence the gamma-globin gene in adult erythrocytes, both Oct-1 and GATA-1 binding are necessary (see p. 7458, second column, end of first complete paragraph), and that even single-nucleotide substitutions in the promoter sequence of the gamma-globin gene can interrupt this process (see whole paper). The teachings of Miller indicate that hemoglobin switching requires coordination of several factors within the cell (p. 90, first sentence). Taken together with the teaching of Liu et al. and Vukicevic et al., it is clear that even subtle changes in sequences of any of the members can be expected to have major consequences on the activity of the system as a whole. Lal et al. (U.S. Patent 6,063,767) teach a protein (SEQ ID NO:3) which is 98.1% identical to the instantly claimed PRO4408 yet there is no evidence that their protein is capable of inducing fetal hemoglobin. Lal et al. contemplate a number of diseases in which their protein is useful (see, for example, column 19, line 54 – column 21, line 42) but nowhere in their long list of diseases are hemoglobin-related disorders mentioned. In fact, increased expression of their protein seems to lead to differentiation of fetal cells (see column 20, lines 63 – 65), whereas the instantly claimed PRO4408 leads to a return to the fetal state (i.e. de-differentiation). If anything, it appears very closely related proteins such as that taught by Lal et al. have the opposite effect of PRO4408. Absent a clear disclosure of which elements of PRO4408 are required for its activity, the claims to fusion proteins and variants that are related only by percentage of sequence identity are not fully enabled.

For these reasons, which include the complexity and unpredictability of the nature of the invention and art in terms of the diversity of proteins and lack of knowledge about functions of encompassed polypeptides structurally related to SEQ ID NO:61, the single working example of PRO4408 protein and its single use without correlation between any structural elements and the asserted functions, the lack of direction or guidance for using either polypeptides that are not identical to SEQ ID NO:61, and the breadth of the claims for structure without function, it would require undue experimentation to use the invention commensurate in scope with the claims.

The examples provided in the specification do not provide a representative number of different amino acid sequences that would enable a representative number of the above discussed sequences with assurances that they possess the desired activity. The mere

recitation of this term, and the definitions provided do not serve as sufficient guidance to enable the breadth of the claims for the various amino acid sequences claimed. See *Ex parte Forman*, 230 USPQ 546. Since the first paragraph of the statute under 35 U.S.C. § 112 requires that there must be an enabling disclosure to support the breadth of the claims, a review of the specification confirms that the scope of the various amino acid sequences that are discussed above have not been enabled. There is but a single amino acid disclosed with reference to PRO4408, SEQ ID NO:61. In the absence of sufficient guidance, it would require undue experimentation to enable a commensurate number of the sequences that are encompassed by the claims.

Claims 22 – 27 and 30 - 34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The deposit of biological organisms is considered by the Examiner to be necessary for enablement of the current invention (see 37 C.F.R § 1.808(a)). Examiner acknowledges the deposit of organisms under accession number ATCC 203018 under terms of the Budapest Treaty on International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure in partial compliance with this requirement. However, in order to be fully compliant with the requirement, applicants must state that the deposit will be maintained for a term of at least 30 years and *at least five (5) years after the most recent request for the furnishing of a sample of the deposit was received by the depository.* See 37 C.F.R. § 1.806.

Claims 22 – 27, 30, 31, 33, and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 22 - 26 are drawn to polypeptides having at least 80%, 85%, 90%, 95% or 99% sequence identity with a particular disclosed sequence. Dependent claims 33 and 34 are drawn to chimeric polypeptides comprising sequences at least 80% identical to the disclosed sequence. The claims do not require that the claimed polypeptide possess any particular

biological activity, and while claims 22 – 27, 30, and 31 recite "the extracellular domain" of the protein, neither the specification nor the drawings indicate which end of the protein is the extracellular end. Furthermore, the claims do not require that the claimed polypeptide and variants have any particular conserved structure, or other disclosed distinguishing feature. The specification discloses that the nucleic acid encoding PRO4408 has (unspecified) homology to the nucleic acids which encode P_R27897, P_R49942, PBP_RAT, CELF40A3_3, D1ONCVO, PC4214, OV16_ONCVO, P_R27718, GEN10789, and OBA5_DROME, however the instant specification fails to indicate the degree of homology or whether the PRO4408 protein has any homology thereto.

The claims do not require the claimed polypeptide to be identical to the disclosed sequence and the claims have no functional limitation. A complete written description of a genus of polypeptides may be achieved by means of a recitation of a representative number of polypeptides, defined by amino acid sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. Given the unpredictability of homology comparisons as noted above, and the fact that the specification fails to provide objective evidence that the additional sequences are indeed species of the claimed genus it cannot be established that a representative number of species have been disclosed to support the genus claim. No activity is set forth for the additional sequences.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of

ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird,* 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF'S were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, polypeptides comprising the sequence of SEQ ID NO:61, but not the full breadth of the claims meet the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22 – 27 and 30 - 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims that recite "the extracellular domain" of the protein are indefinite as no extracellular domain has been described. Therefore, the metes and bounds of the claims cannot be determined. For example, see Claim 22, parts (c) and (d). The specification does not disclose a transmembrane domain, therefore claims that recite an extracellular domain do not make sense. The term "the extracellular domain" is indefinite as it is not clear to which extracellular domain applicant intends to refer. Finally, if the protein had an extracellular domain, the recitation of "the extracellular domain. . .lacking its associated signal sequence" (claim 22, part (d), for example) is indefinite as a signal sequence is not generally considered to be part of an extracellular domain, as signal sequences are cleaved from said domains in the process of secretion from the cell (see Alberts et al., p. 582).

The remaining claims are rejected for depending from an indefinite claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 22 – 25, 33, and 34 are rejected under 35 U.S.C. 102(e) as being anticipated by Lal et al. (U.S. Patent 6,063,767, issued 16 May 2000, effective filing date 28 October 1997). The claims are drawn to polypeptides 80%, 85%, 90%, or 95% identical to SEQ ID NO:61. Dependent claims are drawn to fusion proteins. Lal et al. teach a protein, SEQ ID NO:3, which is 98.1% identical to SEQ ID NO:61, thereby meeting the limitations of claims 22 – 25. Lal et al. teach the production of fusion proteins (column 14, lines 49 – 59), thereby meeting the limitations of claim 33. Lal et al. further expand this teaching to include epitope tags. A list of specific epitope tags is provided in column 19, lines 21 – 27), and Lal et al. teach joining the nucleotide sequence encoding their protein, PLPB, to epitope tags (lines 19 – 21), thereby meeting the limitation of claim 34.

Claims 22 – 25, 33, and 34 are rejected under 35 U.S.C. 102(e) as being anticipated by Lal et al. (U.S. Patent 5,888,742, issued 30 March 1999, filed 28 October 1997). The '767 patent is a divisional of the '742 patent, therefore the specifications and sequence listings are the same. The reasons why the teachings of Lal et al. meet the limitations of the claims are provided in the preceding paragraph.

Claims 22 – 25 are rejected under 35 U.S.C. 102(a) as being anticipated by Bougueleret et al. (WO 99/31236, published 24 June 1999, pages 157 – 158 of the sequence listing).

Bougueleret et al. teach a sequence, SEQ ID NO:225, which is 97.8% identical to SEQ ID NO:61. The prior art sequence meets the limitations of the claims.

Claims 22 – 25 are rejected under 35 U.S.C. 102(e) as being anticipated by Edwards et al. (WO 99/53051, published 21 October 1999, p. 5 – 6 of the sequence listing). Edwards et al. teach a sequence, SEQ ID NO:8, which is 97.8% identical to SEQ ID NO:61. The prior art sequence meets the limitations of claims 22 – 25.

Conclusion

Claims 22 – 27 and 30 – 34 are rejected. Claims 28 and 29 objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on (571) 272-0829. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SHARON TURNER, PH.D.
PRIMARY EXAMINER

Daniel E. Kolker, Ph.D.
March 14, 2005

3-16-05